REMARKS

Entry of the amendment and reconsideration of the claims is respectfully requested. Claims 4-6 have been cancelled without prejudice. Applicants reserve the right to pursue the subject matter of these claims in one or more continuation application.

Claims 1, 7, and 11 have been amended to further clarify the claimed invention. Claims 52-56 are newly presented. Applicants submit the amendment is supported by the specification, including for example at Table 2 on page 11, page 37, lines 20-28, and page 41, lines 17-20, and raises no issues of new matter.

Specification and Sequence Listing

For purposes of clarity and in order to comply with the sequence rules, Applicants have amended the specification and sequence listing to include the nucleic acid sequence and amino acid sequence for OB1 and appropriate sequence identifiers. Nucleic acid sequences and amino acid sequences for OB1 were known. The nucleic acid sequence corresponds to Genbank accession no. M55669, which is disclosed in the specification in Table 2 at page 11. The amino acid sequence corresponds to Genbank accession no. AAA39376, which is cross-referenced by Genbank accession no. M55669 and was submitted to Genbank on the same day as accession no. M55669. A copy of the Genbank records is enclosed. Moreover, Applicants submit that the human sequences were known and enclose the following exemplary Genbank records:AAB32656; and NM_002594.

35 U.S.C. § 112, first paragraph

Claims 1-16 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse this rejection.

Using gene expression profiling technology, Applicants characterized gene expression changes that occur in the pituitary, hypothalamus, fat, liver, and muscle in response to obesity and treatment with exogenous leptin. Using this process, Applicants determined that obesity increases the expression of OB1 and that the administration of leptin decreases the expression of OB1 (Example 10). Applicants disclose that the demonstrated relationship between OB1

expression and leptin is a useful marker for identifying agents for treating obesity and assessing the efficacy of an obesity treatment.

Human response correlates with animal model

The Office Action alleges using a gene identified in experiments with *ob/ob* mice is unpredictable. Citing Popovic et al., Jequier et al., and Gordon et al., the Office Action alleges that the *ob/ob* mouse is not a model for obesity in general and is not predictive of the human physiological or pharmacological response to leptin administration. Applicants respectfully do not agree.

If the particular model is recognized in the art as correlating to a specific condition, then the model should be accepted as correlating unless the Examiner has evidence that the model does not correlate. *In re Brana*, 34 USPQ2d, 1436, 1441 (Fed. Cir. 1995); MPEP § 2164.02. Applicants submit that the art cited in the Office Action does not establish that the human response to leptin does not reasonably correlate with the animal model.

Quoting Jequier et al., the Office Action asserts that humans are resistant to the effects of endogenous leptin and that administration of exogenous leptin to obese human patients does not induce weight loss. Jequier et al. cites Heymsfield et al., 1999, *JAMA*, 282:1568-1575 as support for the statement that administration of exogenous leptin does not induce weight loss. However, in fact, Heymsfield et al. discloses that a statistically significant dose response relationship exists between leptin administration and weight loss after 4 weeks of exposure to recombinant leptin in lean and obese subjects and after 24 weeks of exposure in obese subjects (Heymsfield et al. at page 1573 and Fig. 3) (copy attached). On average, weight loss increased with recombinant leptin dose. Weight loss in subjects treated with recombinant leptin was primarily due to fat loss, which accounted for 95% of the weight lost among obese subjects in the 2 highest-dosing cohorts after 24 weeks. (Heymsfield et al. at page 1573 and Fig. 4).

Applicants disclose that the administration of leptin decreases the expression of OB1 and that the down regulation of OB1 in response to leptin may contribute to the loss of the obese phenotype (Example 10 and specification at page 13, lines 23-25). The results of Heymsfield et al. establish that the human response to leptin correlates with the response to leptin in the animal model. One of skill in the art therefore would have reasonably expected (1) the response of humans to leptin correlates with the response of mice to leptin and (2) the upregulation of PC2 in

ob/ob mice and decrease in expression of PC2 in ob/ob mice in response to leptin indicates PC2 can serve as a biomarker for obesity.

Citing Gorden et al. and Popovic et al., the Office Action asserts that some biological effects of leptin have not been observed in humans and that this suggests that rodent models might not predict human physiological or pharmacological response to leptin administration. This assertion is moot in view of Heymsfield et al., which clearly demonstrates that administration of exogenous leptin to obese human subjects induces weight loss. One of skill in the art would have reasonably expected the response of mice to leptin to correlate with the response of humans to leptin.

The Office Action alleges the combination of Gorden et al. and Takahashi et al. clearly show that the physiological effects of leptin in a single mouse strain cannot be reliably extrapolated to all species of animal. Gorden et al. note that leptin was discovered in a rodent model and that the rodent model might not predict human physiological or pharmacological response to leptin administration. The Office Action asserts this concern is echoed by Takahashi et al. Applicants respectfully do not agree.

Contrary to the assertions in the Office Action, the results in Takahashi et al. merely demonstrate that some mouse strains are more sensitive to leptin than others. Similar to *ob/ob* mice, exogenous administration of leptin to SWR/J mice and C57Bl/6J resulted in weight loss. Subcutaneous injections of leptin decreased the body weight of SWR/J mice by 30 % and the body weight of C57Bl/6J mice by 20% (see Takahashi et al. at Fig. 3b). Therefore, Takahashi et al. validates that exogenous administration of leptin to mice induces weight loss regardless of whether the mice express or do not express endogenous leptin. As discussed above, similar results were obtained by Heymsfield et al. in human subjects. Therefore, Applicants submit one of skill in the art would have reasonably expected (1) the response of humans to leptin to correlate with the response of mice to leptin and (2) the upregulation of PC2 in ob/ob mice and decrease in expression of PC2 in ob/ob mice in response to leptin indicates PC2 can serve as a biomarker for obesity.

The Office Action asserts that the *ob/ob* mice used in the experiments disclosed in the application do not express endogenous leptin, unlike the vast majority of obese humans. Citing Jequier et al, the Office Action asserts obese human subjects have high plasma leptin

concentrations that do not induce the expected effects and that this suggests that obese humans are resistant to the effects of endogenous leptin. Applicants respectfully do not agree.

As discussed above, Takahashi et al. shows exogenous administration of leptin induces weight loss in mice regardless of whether the mice express or do not express endogenous leptin. As discussed previously, humans with high levels of leptin also respond to leptin administration. Weight loss, on average, in obese human patients was found to be dependent on the dose of leptin administered to the patients (Heymsfield et al. at page 1573). Weight loss in human subjects treated with recombinant leptin was primarily due to fat loss, which accounted for 95% of the weight lost among obese subjects in the 2 highest-dosing cohorts after 2 weeks. (Heymsfield et al. at page 1573 and Fig. 4). Heymsfield et al. conclude that the findings do not suggest an absolute leptin resistance, but merely that higher doses of exogenous leptin may be required to provide a sufficient signal for weight loss in subjects with greater adiposity. (See page 1573)Based on the foregoing, Applicants respectfully request withdrawal of the rejection on this basis.

Validation of biomarkers

The Office Action alleges one of skill in the art would have to engage in undue experimentation to establish the expression of OB1 is a valid marker for obesity. Citing Wagner, Frank et al., and Feng et al., the Office Action alleges the art clearly teaches that the utility of a putative biomarker as a surrogate endpoint for any disease state is unpredictable and must be validated in order to be clinically useful. Applicants respectfully do not agree.

Generally, the stage at which a biotechnological or pharmaceutical invention becomes useful is well before it is ready to be used in a clinical setting. *In re Brana*, 34 USPQ2d, 1436, 1443 (Fed. Cir. 1995). Clinical approval is not a prerequisite for enablement (MPEP § 2164.05).

As discussed above, Applicants have provided evidence that the effect of leptin on expression of PC2 in *ob/ob* mice correlates to the expression of PC2 in lean mice. Applicants have also provided that administration of exogenous leptin to obese and lean human results in weight loss, which establishes the mouse model as a valid model for studying the effect of leptin and for identifying leptin sensitive genes. Further, Applicants have described that PC2 is a protease that can cleave POMC which is a hormone that is implicated in obesity. Thus, Applicants have provided more than just upregulation or downregulation of a particular gene in

mouse model, and that the information provided in the specification either alone or in combination with what is known in the art provides a reasonable correlation that PC2 is a biomarker for obesity.

A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka,* 244 USPQ, 739, 747 (Fed. Cir. 1985). Applicants submit the correlation satisfies the enablement requirement. One of skill in the art would have reasonably expected (1) the response of humans to leptin to correlate with the response of mice to leptin and (2) the administration of leptin to decrease the expression of OB1 in obese human subjects as demonstrated by Applicants in the obese mouse model.

Applicants respectfully request withdrawal of the rejection on this basis.

Naggert et al.

The Office Action alleges the general applicability of OB1 expression as a marker for obesity is clearly unpredictable because Naggert et al. reports that there was no change in the expression of PC2 in fat/fat obese mice relative to littermate controls. Applicants respectively do not agree.

Naggert et al discusses a mouse model that is hyperglycemic and has impaired proinsulin processing due to a mutation in carboxypeptidase E. The reference indicates that the cells exhibited an increase in immature granules known to be enriched for prohormone convertases. See column 10, lines 35-42. Although, the reference indicates that using western blot the amount of PC2 was about the same in both genotypes, no actual data is shown and no quantitative or semi quantitative techniques were used to establish that there was no increase in PC2. Moreover, these results seem to contradict the results showing an increase in immature granules. Since Naggert does not provide any evidence concerning an increase or decrease in expression of PC2, the reference does not establish the unpredictability of OB1 expression as a marker for obesity.

Applicants request withdrawal of the rejection on this basis.

Test cell population

The Office Action alleges that practicability of the claimed invention with test cell populations others than pituitary cells remained unknown at the time of filing. The office action alleges that Applicants post filing publication Renz et al., 2000, *J. Biol. Chem.*, 275:10429-10436

stated that is was not known whether the effects of leptin on PC2 expression is limited to particular cell types.Applicants respectfully do not agree.

Applicants submit that it was known to those of skill in the art that POMC and PC2 are expressed in many cells types include hypothalamus, pituitary, skin, spleen cells, circulating white blood cells and pancreatic cells. Applicants submit one of skill in the art would be able to use any of these cells to monitor treatment. Moreover, with respect to identifying a therapeutic agent, the specification provides that any cell type can be utilized to express endogenous or recombinant PC2. (See pages 28-29 in the specification.)

In view of the forgoing, Applicants submit one of skill in the art would be able to practice the claims without undue experimentation.

Applicants respectfully request withdrawal of the rejection

5 U.S.C. § 112, second paragraph

Claim 6 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Without acquiescing to the rejection and solely for the purpose of advancing prosecution, claim 6 has been cancelled without prejudice. Withdrawal of the rejection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date: July 6, 2006

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